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Stimuli-Responsive Hydrogels: An Interdisciplinary Overview

Sudipta Chatterjee and Patrick Chi-leung Hui

Abstract

Stimuli-responsive hydrogels formed by various natural and synthetic polymers are capable of showing distinctive changes in their properties with external stimuli like temperature, pH, light, ionic changes, and redox potential. Some hydrogels are developed to exhibit dual responsiveness with external stimuli such as pH and temperature. The stimuli-responsive hydrogels find a wide variety of biomedical applications including drug delivery, gene delivery, and tissue regeneration. The advanced functionalities can be imparted to textile materials by integrating stimuli-responsive hydrogels into them and stimuli-responsive hydrogels including thermoresponsive, pH-responsive, and dual-responsive improve moisture and water retention property, environmental responsiveness, esthetic appeal, display, and comfort of textiles. Stimuli-responsive hydrogels loaded with various kinds of drugs are applied for textile-based transdermal therapy as these hydrogels as drug carriers show controlled and sustained drug release. In this chapter, drug delivery and textile applications of thermoresponsive, pH-responsive, and dual-responsive (pH and temperature) hydrogels are discussed and analyzed.

Keywords: stimuli-responsive, hydrogel, thermoresponsive, pH-responsive, dual-responsive, textile, drug delivery, transdermal therapy

1. Introduction

Hydrogels are three-dimensional polymeric networks of hydrophilic polymers, and the network structure of hydrogel formed by natural or synthetic polymers is capable of holding a large amount of water in it [1, 2]. Hydrogels show the ability to swell and hold a significant fraction of water within its structures without being dissolved in it [3]. The amount of water in the hydrogel, typically in the swollen state depends on the nature of polymer and also on the polymeric network structure [4]. The hydrophilic functional groups attached to the polymeric backbone of hydrogels impart ability to hold water in its structure, and dissolution in water is resisted because of cross-linking polymeric network structures [5]. Physical hydrogels are “ionotropic” reversible hydrogels showing disintegration by changes in the external environmental conditions such as ionic strength, pH, and temperature [6]. Physical hydrogels are formed by the interaction between oppositely charged polyelectrolytes or oppositely charged multivalent ion/surfactant and polyelectrolyte [7]. Chemical hydrogels are formed from covalently cross-linked polymeric network having permanent junctions [8]. Hydrogels are capable of swelling and shrinking reversibly in response to changes in the external environment [9]. Homo-polymeric hydrogels are made of only polymer, whereas copolymeric or multi-polymeric hydrogels are

made of two or more polymers [1]. Hydrogels can be modified in terms of chemical structure, composition, biological functions, biodegradability, and various physicochemical properties such as mechanical and rheological, spectral, and pH stability, and release and loading properties for drugs can be managed to optimize the performances of the hydrogels in multiple dimensions especially for biomedical applications [4, 10, 11]. Hydrogels find a wide range of pharmaceutical and biomedical applications due to their resemblance with the physical properties of living tissues such as high water content, compactness, and low interfacial tension with aqueous media [12–14]. The compactness of hydrogels in aqueous media is maintained by physical cross-linking (e.g., entanglements, crystallites) and chemical cross-linking [15]. Hydrogels are found in the form of matrix, film, microsphere, and nanoparticles depending on the processing parameters of hydrogels [16, 17]. Nowadays, hydrogels are being practically applied for drug delivery, tissue engineering, self-healing process of the body and also as biosensors and hemostasis bandages [18–22]. Hydrogels are being used for developing drug delivery systems as they are possessing good transport properties for drugs and capable of protecting drugs from the external environment, and modifications on the gel structures can be easily introduced according to the route of administration [2].

During the last few decades, a significant amount of research has been performed to develop hydrogels with stimuli-responsive properties where external triggers like temperature, pH, light, magnetic and electrical fields, shear forces, and chemicals cause some changes in the properties of the hydrogel materials such as swelling, porosity, physical structure, and modulus [23–25]. Stimuli-responsive hydrogels are capable of showing switchable sol-gel transition upon application of external triggers. The external stimuli including temperature, light, magnetic and electrical fields, and ultrasonic wave are considered physical triggers, while pH, redox reactions are considered chemical triggers [26]. This stimuli-responsive behavior of hydrogels has opened immense possibilities of extremely diversified applications in biomedical areas especially for drug delivery applications [27–30]. Thermoresponsive hydrogels show changes in mechanical and drug release properties with the change in the temperature of the external environment [31, 32]. The schematic representation of formation of drug-loaded thermoresponsive hydrogel as drug delivery system has been given in **Figure 1**.

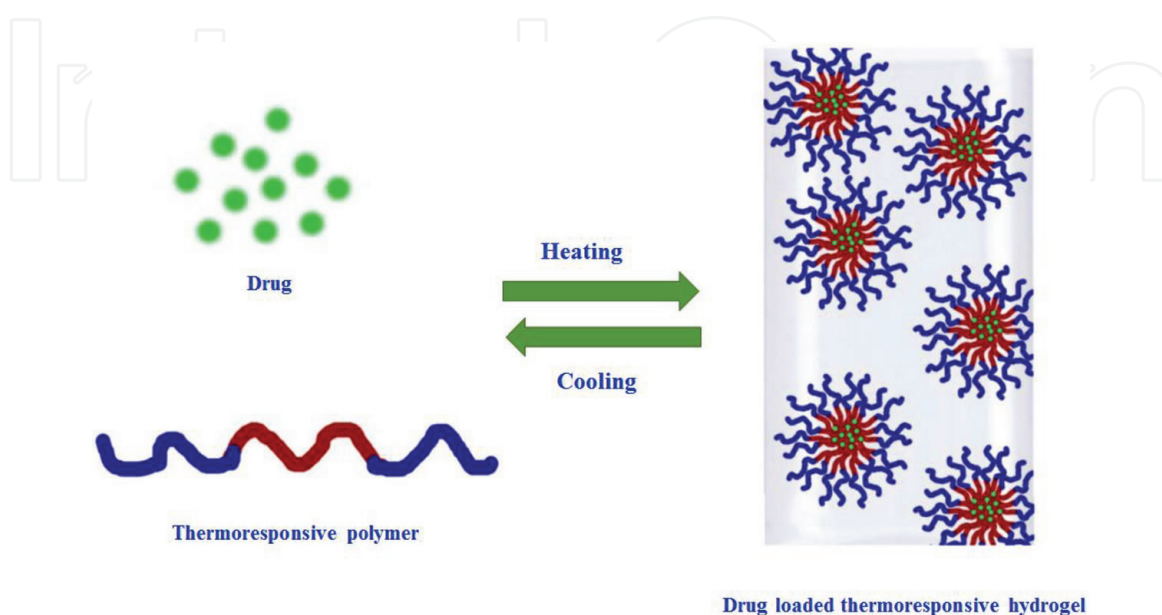


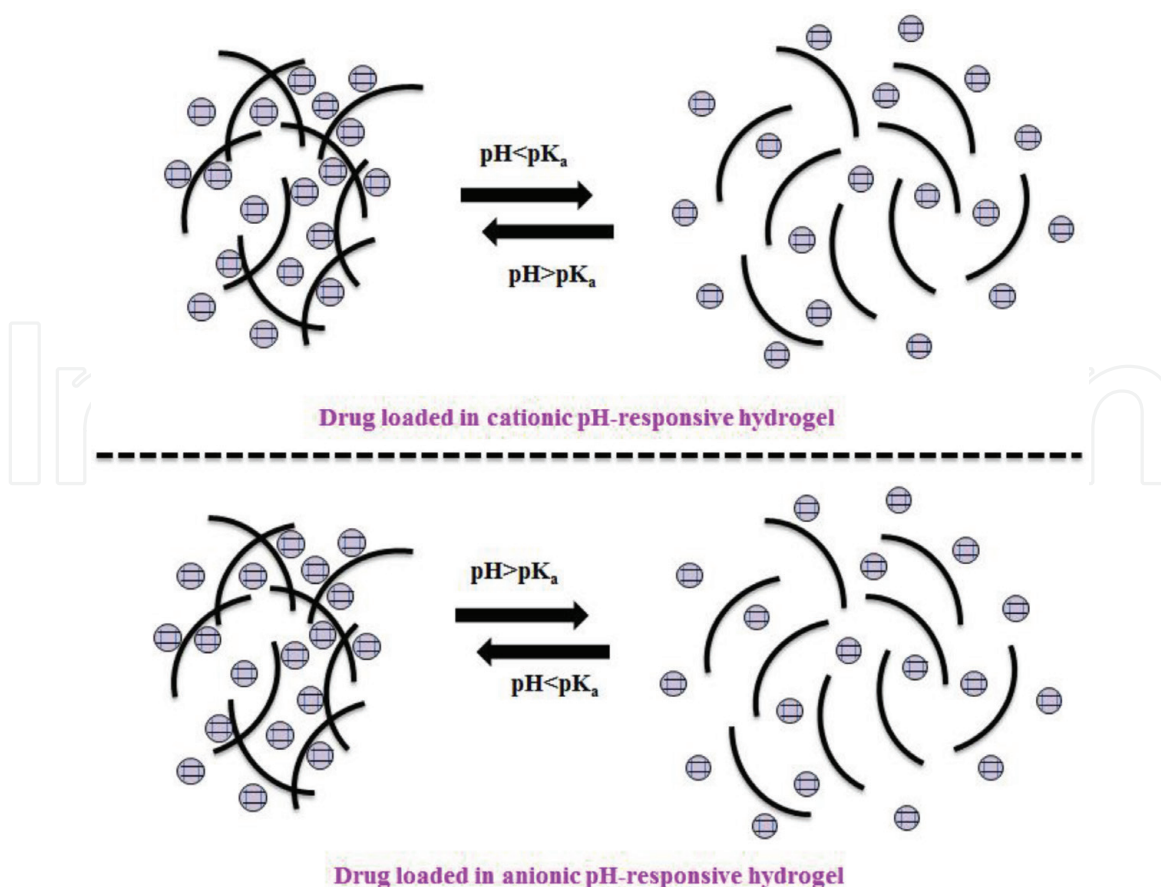
Figure 1.

The schematic representation of thermoresponsive hydrogel formation loaded with drug using temperature as a stimulus.

Thermoresponsive hydrogels are formed above a low critical solution temperature (LCST) where the polymer solutions undergo phase separation to form hydrogels [28, 33]. At temperature below LCST, all the components in the system are completely miscible in all proportions [34]. Polymers with upper critical solution temperature (UCST) get soluble upon heating [35]. The thermoresponsive hydrogels are found to have various hydrophobic groups, and LCST/UCST can be modified by changing the ratio of hydrophilic and hydrophobic groups of the polymers [36, 37]. Thermoresponsive hydrogels are of great interest in the area of biomedical applications especially for drug delivery applications as many hydrogels show gel formation at universally accepted physiological temperature of 37°C, and also, several easy modifications are available to control gel formation at physiological temperature [23, 25, 38–40]. In situ forming hydrogels find biomedical applications as it can provide suitable ways for simple, “custom-made diagnostics” [13]. pH-responsive hydrogels show swelling/shrinking behavior in response to change in the environmental pH [41, 42], and this class of stimuli-responsive hydrogels is of particular interest for biomedical applications as substantial pH changes are found in various organs or locations in the body required for normal body function such as the gastrointestinal tract [43], blood vessels, intracellular vesicles [44], and female genital tract [45]. pH changes within the body also occur due to abnormal body functions or in the diseased state including tumor environment [46] and inflammation [47]. The pH-responsive hydrogel systems have been widely used for developing a wide variety of drug delivery systems [41, 48–50].

Thermoresponsive hydrogels are made from a wide variety of natural and synthetic polymers, and some thermoresponsive hydrogels forming polymers find a lot of interests as these hydrogels have excellent biomedical applications especially for developing drug delivery systems used in cancer therapy, transdermal drug therapy, and oral drug delivery [25, 35, 51, 52]. The thermoresponsive polymers widely used in developing drug delivery systems are poly(*N*-isopropylacrylamide) (pNIPAAm); pluronics® or poloxamers mainly pluronic F127 (PF127), polyoxazoline, and poly(organophosphazenes); and some natural polymers having thermoresponsive properties are gelatin/collagen, cellulose, chitosan, xyloglucan, starch, xanthan gum, carrageenans, hyaluronic acid, dextran, poly(γ -glutamate), and elastin and elastin like polypeptide/oligopeptide [53–55]. The most commonly used polymers to develop pH-responsive behavior in hydrogels include either acidic groups (carboxylic) or basic groups (amino), and the monomers used in pH-responsive polymers are acrylic acid, acrylamide, methacrylic acid, dimethylaminoethyl methacrylate, diethylaminoethyl methacrylate, and ethylene glycol [46, 56]. All pH-responsive polymers contain pendant acidic or basic groups that either accept or donate protons in response to pH change in the external environment [57, 58]. The pendant ionizable groups of anionic hydrogel networks become ionized in solutions at a pH greater than their acid dissociation constant (pKa), and cationic hydrogel networks swell at pH lower than their pKa values as their pendant groups get ionized in that pH. The swelling and shrinking behavior of pH-responsive hydrogels depending on the charge of pH-responsive polymer is schematically presented in **Figure 2**. Natural polymers including chitosan, gelatin, alginate, and albumin can also show pH-responsive behavior [41, 59, 60]. pH-responsive hydrogels made from synthetic and natural polymers are widely used in drug delivery applications [23].

Stimuli-responsive polymers are used as surface modifying systems of textile fabrics to enrich them with advanced functionalities and environmental responsiveness [61]. Thermoresponsive/pH-responsive or any other stimuli-responsive hydrogel present on textile fabric is capable of responding to changes in environmental conditions and giving comfort by actively balancing body temperature and moisture [53]. Stimuli-responsive (thermoresponsive) hydrogels are used as drug

**Figure 2.**

The schematic representation of swelling/shrinking of pH-responsive hydrogels.

delivery systems for the controlled release of drugs from functionalized textiles applied for skin care [53, 61]. Thereby, drug delivery systems from hydrogels of stimuli-responsive polymers are being developed for textile-based transdermal therapy [61]. The functionalized textiles with stimuli-responsive hydrogels also include esthetic appeal, soft display, wound monitoring, smart wetting properties, and protection against extreme variations in environmental conditions [61].

2. Drug delivery and textile applications of thermoresponsive polymers

A wide variety of natural and synthetic polymers and their derivatives are capable of exhibiting thermoresponsive gelation, and during the last two decades, many drug delivery systems for cancer therapy, tissue regeneration, transdermal drug therapy, and oral drug delivery are developed using thermoresponsive polymers [25, 62]. Thermoresponsive hydrogel-based drug delivery systems have been increasingly gaining attention as thermoresponsive hydrogels can effectively encapsulate drugs and release them in a sustained manner [63]. Also, various methods and easy modifications on both natural and synthetic thermosensitive polymers can be introduced to tailor thermosensitive hydrogel properties in order to achieve the desired drug release profile [64–66]. Several chemical modifications are applied on thermoresponsive polymers to improve stability and drug release properties of the hydrogels [36, 38].

Poly(*N*-isopropylacrylamide) (pNIPAAm) and its copolymers can form thermoresponsive hydrogels which are widely used for developing drug delivery systems with excellent applicabilities and functionalities [67–71]. pNIPAAm shows LCST (32°C) near body temperature in pure water and becomes hydrophobic at the LCST

[72, 73]. pNIPAAm was copolymerized with acrylamide [74] and N-(2-(dimethylamino)ethyl) methacrylamide [75] to work more effectively at body temperature as thermoresponsive hydrogel-based drug delivery systems. The hydrogel made of pNIPAAm and methyl cellulose combined thermoresponsive properties of both materials and LCST of the compound varied with the proportion of constituents forming hydrogel [16]. Also, methyl cellulose addition to pNIPAAm enhanced the mechanical strength of the hydrogel [16]. The thermoresponsive hydrogel system made of pNIPAAm and butyl methacrylate (BuMA) showed a sustained zero-order drug release and showed gelling near body temperature [76]. The thermoresponsive hydrogel made of copolymers of NIPAAm and propylacrylic acid (PAA) by reversible addition-fragmentation chain transfer (RAFT) polymerization method showed tunable properties in a variety of molecular switching and drug delivery applications [77]. This copolymer of NIPAAm and propylacrylic acid (PAA) also showed pH-responsive behavior which is relevant for drug delivery applications [77]. The nanoparticle hydrogel system made of pNIPAAm and a photo cross-linker, poly(ethylene glycol) diacrylate (PEG-DA) showed thermoresponsive hydrogel forming property and was capable of showing in situ photopolymerization to localize at a specific location in the body [78]. The thermoresponsive hydrogel made from copolymer of alginate and pNIPAAm was used as a drug delivery system for anticancer drug doxorubicin [79]. The hydrogel formed from alginate and pNIPAAm showed gel formation at body temperature of 37°C [79]. Thermoresponsive hydrogels made pNIPAAm and poly(ethylene glycol) diacrylate (PEG-DA) were used as ocular drug delivery systems to deliver some bioactive proteins and immunoglobulin G (IgG) [80]. In spite of various drug delivery applications of pNIPAAm-based thermoresponsive hydrogels, there is a doubt on biodegradability of this polymer as it is very relevant to successful and safe drug delivery applications. Nowadays, a wide number of researches are being performed to develop biodegradable copolymers of pNIPAAm. The most promising polymers for biodegradability enhancement of pNIPAAm hydrogels are reported to be poly(ethylene glycol) (PEG) and/or poly(ϵ -caprolactone) (PCL) [81]. Moreover, the biocompatibility of pNIPAAm-based thermoresponsive hydrogels is mostly achieved by copolymerizing with PEG and/or PCL [81]. A dual-responsive spiropyran-NIPAAm hydrogel (light and temperature) formed by a facile and versatile surface-initiated controlled polymerization method (SI-ARGET-ATRP) showed capability of dimensional changes on cotton fabric upon irradiation with visible light or a temperature stimulus [82]. pNIPAAm-based thermoresponsive hydrogels were applied to develop smart functionalized textiles [61]. The dual-responsive nano-hydrogel made of pNIPAAm and chitosan was applied on cotton fabric as a surface modifying system using 4-butane tetra carboxylic acid (BTCA) as an environmental friendly cross-linking agent [83]. The use of nano-hydrogel on cotton fabric enhanced its water retention capacity [83]. Thermoresponsive hydrogel made of pNIPAAm and polyurethane hydrogel via chitosan modification exhibited antibacterial function against *Staphylococcus aureus* and *Escherichia coli* on nonwoven fabric [84]. pNIPAAm-based thermoresponsive hydrogel applied on fabrics can exhibit reversible swelling/shrinkage and modify water absorption/retention capacity [61].

Another important thermoresponsive polymer pluronic F127 (PF127) is capable of forming hydrogel near body temperature, and PF127 is a triblock copolymer of poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) (PEO-PPO-PEO) [25, 85]. In order to enhance applicability and functionality of PF127-based drug delivery systems, various chemical modifications were done on PF127 [86–88]. The thermoresponsive hydrogel made from PF127 and glycol chitosan was used as drug delivery system for doxorubicin and partially for superoxide dismutase (SOD) [89].

Thermoresponsive hydrogel made from PF127 and hyaluronic acid was used as drug delivery system for human growth hormone [90]. The conjugate was made by photopolymerization, and it formed hydrogel near body temperature [90]. The thermoresponsive hydrogel made from PF127, polyurethane, and Erythrosin B was used as drug carriers and fluorescence imaging probes in biomedical applications as well [91]. The hydrogel also showed pH responsiveness [91]. The thermoresponsive hydrogel microspheres from PF-127 and chitosan cross-linked with glutaraldehyde as a cross-linker were applied for delivery of anticancer drug 5-fluorouracil [92]. Thermoresponsive hydrogels made from PF127-based were used for textile-based transdermal drug delivery [53, 93]. Chinese herbal medicine-loaded PF127-based thermoresponsive hydrogels were applied for textile-based transdermal therapy [94, 95]. The drug-loaded hydrogels developed by a “cold method” were capable of moisturizing the skin and protecting it against the pathogenesis of atopic dermatitis [94, 95]. Thermoresponsive hydrogel system from PF127 and alginate was applied for transdermal delivery of selegiline and the thermoresponsive hydrogel synthesized either by physical mixing of components or chemical grafting showed sustained and controlled release of selegiline [96].

Thermoresponsive hydrogels based on poly(ethylene oxide)-based diblock/triblock copolymers were successfully applied as drug delivery systems [36]. Thermoresponsive hydrogels made of poly(ethylene oxide)-poly(ϵ -caprolactone) [PEO-PCL] diblock copolymers [97] and poly(ethylene oxide)-poly(ϵ -caprolactone)-poly(ethylene oxide) [PEO-PCL-PEO] triblock copolymers [98] were used as drug delivery systems. Thermoresponsive hydrogel from [PEO-PCL-PEO] triblock copolymers were coated on nonwoven textile fabric to develop functionalized textile fabric with moisture management property [99]. The hydrogel showed thermoresponsive property with LCST (34°C) close to body temperature and also exhibited controlled and sustained release of drug [99].

Some natural polymers capable of forming thermoresponsive hydrogels and drug delivery systems formed from biopolymer-based thermoresponsive hydrogels find excellent clinical applications [25]. Methylcellulose, water-soluble cellulose derivative, is capable of forming thermoresponsive hydrogels and forms thermoreversible hydrogel in the temperatures range of 60–80°C [25]. The gelation of methylcellulose involves hydrophobic association of polymer molecules and then their phase separation to form gel [100]. Water-soluble methylcellulose was developed by substituting hydroxyl groups on cellulose with more hydrophobic methyl units, and solubility of methylcellulose in water was affected by the degree of substitution [100]. The copolymer of methylcellulose and pNIPAAm combined the thermogelling properties of both materials, and mechanical strength of the hydrogel was enhanced after combining methylcellulose with NIPAAm [101]. The micelle-based thermoreversible gel system from methylcellulose and PF127 exhibited sustained delivery of docetaxel for more than 30 days which resulted in enhanced anticancer effect of docetaxel compared to the free drug [102]. Thermoresponsive hydrogel made of carboxymethyl cellulose and gelatin-loaded with lidocaine was applied for transdermal drug therapy [103]. Thermoresponsive hydrogel system made of PF127 and carboxymethyl cellulose sodium was used as textile-based transdermal drug delivery system with the Chinese herbal medicine (cortex moutan) for the treatment of atopic dermatitis (AD) [94, 95]. This drug delivery system provided both moisture and drug to the skin protecting pathogenesis of AD [94, 95].

Chitosan produced by the deacetylation of chitin is used to form thermoresponsive hydrogels for biological applications [25]. The commercial

source of chitin is the exoskeleton of shrimp, lobster, and insects, and chitin is converted to more biologically active chitosan using alkali treatment. As chitosan lacks intrinsic thermosensitive properties, thus, other thermosensitive materials need to be introduced into chitosan to make it work as thermoresponsive hydrogels [53]. Chitosan-pluronic (CP) thermoresponsive hydrogel was formed by grafting pluronic onto chitosan using carbodiimide chemistry, and the hydrogel was designed as an injectable cell delivery system for cartilage regeneration [104]. The thermoresponsive hydrogel system using chitosan, hyaluronic acid, and NIPAAm was used as drug delivery system for the analgesic drug nalbuphine, and it showed better controlled release of the drug in vitro than that of hydrogel made of only pNIPAAm hydrogels [105]. Carboxymethyl chitosan-modified pluronic thermoresponsive hydrogel was used for localized delivery of paclitaxel (PTX) [106]. The mechanical strength of the thermoresponsive hydrogel was increased after cross-linking carboxymethyl chitosan with glutaraldehyde, and also the drug delivery system showed sustained drug delivery at the tumor sites [106]. The thermoresponsive hydrogels were made from pNIPAAm and chitosan by interpenetrating polymer network (IPN) technology using a redox initiator system made of potassium peroxydisulfate and sodium hydrogen sulfite [107]. The hydrogel system was applied on cotton fabric using glutaraldehyde as cross-linker to enhance the thermoresponsive behavior and antibacterial activity of cotton fabric [107].

Dextran is a complex-branched glucan made of glucose monomers and synthesized from sucrose by bacterial fermentation using lactic acid bacteria *Leuconostoc mesenteroides* and *Streptococcus mutans*. Thermoresponsive hydrogel system from poly(ϵ -lysine)-grafted dextran and α -cyclodextrins showed also pH-responsive character and could be used as drug delivery system [108]. The block polymers consisting of dextran, 2-hydroxyethyl methacrylate, oligolactate, and NIPAAm were capable of forming thermoresponsive and completely biodegradable hydrogels which showed LCST near body temperature (around 32°C) and exhibited controlled release of incorporated albumin at environmental temperatures [109]. The multifunctional and biodegradable thermoresponsive hydrogels made from NIPAAm, dextran, and poly(L-lactic acid) were used as drug delivery systems, and it showed gelation (LCST) around 32°C [110].

Xyloglucan, a major component of higher plant cell wall is commercially obtained from tamarind seed (*Tamarindus indica*) and made of a β -1,4 linked D-glucan backbone where α -D xylopyranose residues are partially substituted on O-6 position of glucopyranosyl residues. The thermoresponsive behavior of xyloglucan arises after elimination of 35% of its galactose residues, and thermoresponsive hydrogels of xyloglucans have been studied for drug delivery applications [25]. Xyloglucan (3%wt.) in aqueous media after gelation showed three-dimensional macroporous interconnected network with an elastic modulus which was significantly higher than other natural or synthetic hydrogels [111]. β -galactosidase-treated xyloglucan after being partially degraded (45% of galactose residues removed) formed thermoresponsive hydrogel at 27°C to work as drug delivery system for nasal drugs [111]. Xyloglucan-based thermoresponsive hydrogel was developed for delivery of lidocaine HCl in the treatment of periodontitis, and this in situ hydrogel-loaded with analgesic drug offered an alternative to painful injection therapy of anesthesia during dental surgery [112].

The chemical nature and biomedical applications of thermoresponsive hydrogels are briefly summarized in **Table 1**.

Chemical constituents of thermoresponsive hydrogel	Biomedical application of thermoresponsive hydrogel	References
pNIPAAm, butyl methacrylate	Drug delivery application	[76]
NIPAAm, propylacrylic acid	Drug delivery application	[77]
pNIPAAm, polyurethane, chitosan	Textile application (antibacterial)	[84]
PF127, glycol chitosan	Drug delivery application	[89]
PF127, hyaluronic acid	Drug delivery application	[90]
PF127, carboxymethyl cellulose sodium	Textile application (drug delivery and moisture management)	[94, 95]
PEO, PCL	Drug delivery application	[97, 98]
PEO, PCL	Textile application (moisture management)	[99]
Methylcellulose, PF127	Drug delivery application	[101, 102]
Carboxymethyl cellulose, gelatin	Drug delivery application	[103]
Chitosan, pluronic	Drug delivery application	[104]
Chitosan, PF127	Textile application (antibacterial)	[107]
Dextran, poly(ϵ -lysine, α -cyclodextrin	Drug delivery application	[108]
Xyloglucan	Drug delivery application	[112]

Table 1.
The chemical nature and biomedical applications of thermoresponsive hydrogels.

3. Drug delivery and textile applications of pH-responsive polymers

Anionic hydrogel network formed by polyacrylic acid (PAA) was applied as pH-responsive hydrogel system as it swelled/dissolved at high pH of the upper small intestine of the gastrointestinal (GI) tract but resisted any swelling or remained collapsed while in the acidic pH of the stomach, and thereby, as a drug delivery system, it protected loaded drug from any harsh acidic environment in the stomach [43, 113]. PAA-based pH-responsive biodegradable hydrogels were developed from four types of pH-sensitive PAA derivatives and a biodegradable poly(l-glutamic acid) cross-linker and applied as drug delivery systems for oral delivery of insulin [114]. The wound healing monitoring textiles were developed from pH-responsive hydrogel of polyvinyl acetate cross-linked PAA, and the swelling of the pH-responsive hydrogel resulted in a refractive index change of the hydrogel providing information on the stage of wound healing process [115].

Albumin is a natural protein harvested directly from the human blood plasma, and hydrogels developed from serum albumin are widely applied for drug delivery applications [26]. Albumin formed pH-responsive anionic hydrogel network which swelled in basic pH medium, and pH responsiveness of albumin was developed through reductive reaction followed by oxidative refolding [116]. Furthermore, the albumin hydrogel also showed redox responsiveness. An increase in albumin concentration in the hydrogel enhanced its mechanical and structural stability and improved biodegradability and biocompatibility [116]. The use of the hydrogel as drug delivery system for tetracycline showed its usefulness in drug delivery applications [116]. pH-responsive hydrogel based on bovine serum albumin (BSA) derivative was applied for oral drug delivery, and free radical polymerization technique was applied to develop methacrylate derivatized BSA [117]. Medical textiles for wound healing included coating of BSA hydrogels on textile materials [118].

Poly(ethylene glycol) (PEG) is a highly water-soluble nonionic polymer and widely used in drug delivery applications because of its biocompatibility and low toxicity. The pH-responsive hydrogel made of PEG derivative and α,β -polyaspartylhydrazide loaded with doxorubicin was applied for cancer therapy [46]. It remained as free-flowing fluid before injection but spontaneously changed into a semisolid hydrogel just after injecting into the body [46]. The prepared hydrogel was biocompatible and biodegradable and utilized as a pH-responsive vector for drug delivery [46]. pH-responsive hydrogels made of poly(itaconic acid) with PEG were applied as drug delivery system for oral drug delivery and the hydrogels were prepared by UV-initiated free radical polymerization using tetraethylene glycol as the cross-linking agent and Irgacure 2959 as the initiator [119]. Medical textiles developed from coating pH-responsive hydrogel made of PEG and chitosan on cotton membrane were applied for wound dressing [120].

pH-responsive cationic hydrogels using polymers like poly(dimethylaminoethyl methacrylate) (PDMAEMA) and poly(diethylaminoethyl methacrylate) (PDEAEMA) show swelling in low pH due to the protonation of their tertiary amine groups [121]. Because of pH responsiveness and ability to bind with anionic hydrogels, cationic hydrogels find a wide variety of biomedical application especially for drug delivery [122, 123]. pH-responsive hydrogel-based drug delivery system from poly(vinyl alcohol) and PDMAEMA showed promising drug delivery application, and the molecular weight of PDMAEMA was reported to have significant effect on the structure, swelling ratio, and drug release behaviors of the hydrogels at different pH conditions [124]. A pH-responsive nano-hydrogel was synthesized by copolymerization of PDEAEMA with hetero-bifunctional PEG bearing a 4-vinylbenzyl group at one end and a carboxylic acid group at the other end, and nano-hydrogel was found suitable for endosomal release of anticancer drug doxorubicin [125]. The doxorubicin-loaded nano-hydrogel showed much higher drug in pH 5.3 than that in pH 7.4 [125]. Medical textiles were developed by grafting PDMAEMA onto the cotton surface for low-adherent wound dressing [126].

Chitosan is an excellent example of pH-responsive natural polymer having antibacterial activity, biocompatibility, and biodegradability and a wide range of good biological activities [53]. The pH-responsive behavior of chitosan comes from its primary amine groups which can be protonated/deprotonated depending on pH of the external environment (solutions) [127]. Chitosan forms cationic hydrogel network in water which swells in acidic pH and remains collapsed in basic pH, and thereby, the pH-responsive behavior of chitosan-based hydrogels can be controlled for targeted gastrointestinal delivery of a variety of drugs [23]. pH-responsive hydrogel formed from chitosan and poly(ethylene oxide) was used for oral delivery of antibiotics metronidazole and amoxicillin [128]. The hydrogel network swelled more in simulated gastric fluid than simulated intestinal fluid, and also, the drugs were release more from the hydrogel in gastric pH condition than intestinal pH condition [128]. Physically cross-linked pH-responsive hydrogel with enhanced mechanical strength was developed from chitosan, acrylic acid, (2-dimethyl-amino) ethyl methacrylate via in situ free radical polymerization for controlled drug delivery of bovine serum albumin, and 5-fluorouracil in cancer therapy [129]. The potential drug carrier from pH-responsive hydrogel of carboxymethyl chitosan and PEG was developed using photo-induced synthesis, and the release of 5-fluorouracil from the hydrogel was investigated [130]. Smart textile fabrics and medical textiles were developed by integrating pH-responsive chitosan hydrogels onto fabrics [131–133].

The chemical nature and biomedical applications of pH-responsive hydrogels are briefly summarized in **Table 2**.

Chemical constituents of pH-responsive hydrogels	Charge of pH-responsive hydrogel	Biomedical application of pH-responsive hydrogel	References
PAA, poly(l-glutamic acid)	Anionic	Drug delivery application	[114]
PAA, polyvinyl acetate	Anionic	Textile application (wound healing monitoring)	[115]
Albumin	Anionic	Drug delivery application	[116]
BSA, methacrylate	Anionic	Drug delivery application	[117]
BSA	Anionic	Textile application (medical textiles)	[118]
PDMAEMA, poly(vinyl alcohol)	Cationic	Drug delivery application	[124]
PDMAEMA	Cationic	Textile application (medical textiles)	[126]
Chitosan, poly(ethylene oxide)	Cationic	Drug delivery application	[128]
Carboxymethyl chitosan, PEG	Cationic	Drug delivery application	[130]
Chitosan, PEG	Cationic	Textile application (medical textiles)	[120]
Chitosan	Cationic	Textile application (medical textiles)	[131, 132]

Table 2.
The chemical nature and biomedical applications of pH-responsive hydrogels.

4. Drug delivery and textile applications of dual-responsive (pH and temperature) hydrogels

The hydrogel system combined both pH-responsive polymer and thermoresponsive polymer-enhanced efficiency of stimuli-responsive hydrogels for drug delivery applications [134]. The swelling behavior of dual-responsive (pH and temperature) hydrogel has been schematically represented in **Figure 3**.

Natural polymer like chitosan was used as pH-responsive polymer to combine with thermoresponsive synthetic polymer pNIPAAm in order to create dual-responsive (pH and temperature) hydrogel-based drug delivery systems [135–137]. Dual-responsive hydrogels based on glycidyl methacrylated chitosan and pNIPAAm via photopolymerization were used as drug delivery systems for

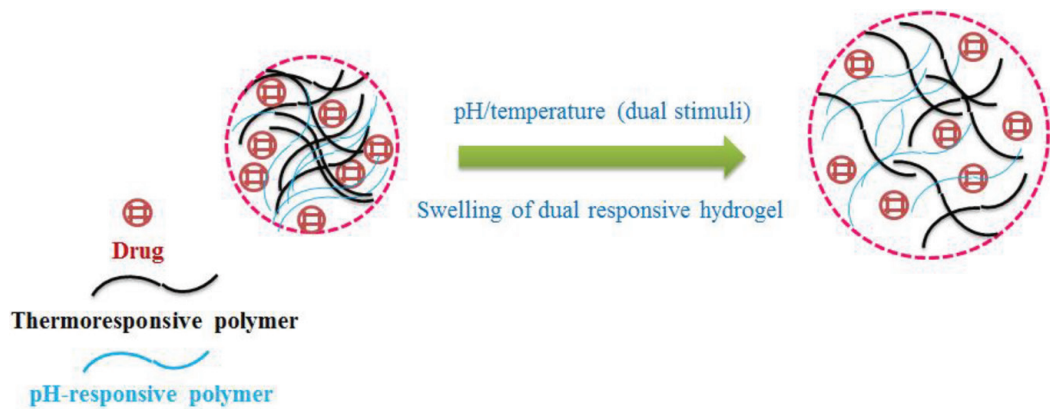


Figure 3.
The schematic representation of swelling/shrinking of dual-responsive (pH and temperature) hydrogels.

acid orange 8 (AO8) and 5-fluorouracil (5-Fu), and the hydrogels showed response to both temperature and pH as external stimuli [135]. Chitosan and pNIPAAm formed dual (pH/temperature)-responsive hydrogel network with semi-interpenetrating polymeric network via radical-induced polymerization of NIPAAm in the presence of chitosan using tetraethyleneglycoldiacrylate as a cross-linker, and this dual-responsive hydrogel was used as drug delivery system for pilocarpine hydrochloride [136]. Dual-responsive hydrogels based on pH-responsive chitosan and temperature responsive pNIPAAm were applied on textile fabrics (cotton fabrics) to modify their surface properties, and these functionalized textiles showed advanced functionalities and environmental responsiveness [83, 138, 139]. Surface modification of cotton fabric with pH and temperature dual-responsive hydrogels of chitosan and pNIPAAm improved air and moisture management activities of functionalized textiles [83].

Dual-responsive hydrogels made of pNIPAAm as thermoresponsive polymer and PAA as pH-responsive polymer found drug delivery applications [77, 140]. The hydrogel system made from copolymer of NIPAAm and itaconic acid [NIPAAm-co-itaconic acid] showed dual responsiveness to external stimuli temperature and pH and was proposed as effective drug delivery system [141]. Dual hydrogel system made of pNIPAAm and PDMAEMA by the combination of atom transfer radical polymerization, reversible addition-fragmentation chain transfer polymerization, and click chemistry showed dual responsiveness for temperature and pH, and this dual-responsive hydrogel was used as drug delivery system for ceftriaxone sodium [142, 143]. Dual-responsive biodegradable hydrogel made from thermoresponsive copolymer p(NIPAAm-co-hydroxyethyl methacrylate) and pH-responsive poly(L-glutamic acid) was applied as drug delivery system for hydrophilic drugs [144]. Dual-responsive (pH and temperature) hydrogel system was developed using thermoresponsive polymer pNIPAAm and cellulose nanofibril isolated by 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO)-mediated oxidation and applied as carrier for drug [145]. Dual-responsive (pH and temperature) hydrogels made from synthetic polymers pNIPAAm and vinyl-capped polyurethane were graft copolymerized onto nonwoven cellulose/PET fabric by ammonium persulfate initiation to modify surface properties of textile material [146]. Dual-responsive hydrogels made of pNIPAAm and polyurethane were grafted onto nonwoven fabric for modifying surface property of textile materials [147].

Chitosan-coated alginate hydrogel beads with pNIPAAm showed pH and temperature dual responsiveness and were applied as drug delivery system with improved encapsulation efficiency and sustained drug release property [148]. The hydrogel consisting of sugarcane bagasse cellulose, carboxymethyl cellulose, and pNIPAAm was applied as a dual-responsive (pH and temperature) drug carrier for BSA, and the drug carrier system showed sustained release of drug [149]. Cellulose-based dual-responsive (pH and temperature) hydrogel was prepared from carboxymethyl cellulose and hydroxyethyl cellulose in an aqueous medium using citric acid (CA) as a cross-linking agent and applied on knitted cotton fabric to modify its surface properties [150]. Chitosan with other biopolymers including β -cyclodextrin (β -CD), arabic gum, guar gum, and pullulan formed four different types of dual-responsive (pH and temperature) hydrogels using glycidoxypolytrimethoxysilan as a cross-linker, and depending on the nature of biopolymers used in hydrogels, the texture of the hydrogels varied [151]. All the varieties of hydrogels were applied on textile fabrics to modify surface properties like antibacterial, water uptake, and moisture retention, and the hydrogels imparted hydrophobicity to the cotton fabric [151].

The chemical nature and biomedical applications of dual-responsive (pH and temperature) hydrogels are briefly summarized in **Table 3**.

Chemical constituents of dual-responsive hydrogel	Biomedical application of dual-responsive hydrogel	References
pNIPAAm (<i>temperature</i>), glycidyl methacrylated chitosan (<i>pH</i>)	Drug delivery application	[135]
pNIPAAm (<i>temperature</i>), chitosan (<i>pH</i>)	Drug delivery application	[136]
pNIPAAm (<i>temperature</i>), chitosan (<i>pH</i>)	Textile application (water and moisture management)	[138, 139]
pNIPAAm (<i>temperature</i>), PAA (<i>pH</i>)	Drug delivery application	[77, 140]
pNIPAAm (<i>temperature</i>), PDMAEMA (<i>pH</i>)	Drug delivery application	[142, 143]
p(NIPAAm-co-hydroxyethyl methacrylate) (<i>temperature</i>), poly(L-glutamic acid) (<i>pH</i>)	Drug delivery application	[144]
pNIPAAm (<i>temperature</i>), vinyl-capped polyurethane (<i>pH</i>)	Drug delivery application	[146]
pNIPAAm (<i>temperature</i>), polyurethane (<i>pH</i>)	Textile application	[147]

Table 3.
The chemical nature and biomedical applications of dual-responsive (pH and temperature) hydrogels.

5. Conclusions

Stimuli-responsive hydrogels from a wide variety of natural and synthetic polymers provide a significant contribution in biomedical area especially for drug delivery applications. Over the last 10 years, the potential applications of stimuli-responsive hydrogels in textiles are rapidly advancing. Functionalized textiles integrated with stimuli-responsive hydrogels show improved moisture/temperature management, esthetic appeal, soft display, and enhanced protection against extreme environmental conditions. Stimuli-responsive hydrogels used in textiles are mainly thermoresponsive, pH-responsive, and furthermore dual-responsive (temperature and pH) in nature, and specific drug-loaded stimuli-responsive hydrogels are being applied for textile-based transdermal therapy. The polymers used in thermoresponsive hydrogels vary from synthetic polymers to nature polymers, and often, composites are developed for better functionalities. pH-responsive hydrogels include natural to synthetic polymers, and depending on the charge of polymers, the charge of pH-responsive hydrogel varies. For site-specific delivery of drug by pH-responsive hydrogels, the charge of hydrogels plays a significant role. Dual-responsive hydrogel includes both thermoresponsive polymer and pH-responsive polymer to show response to external pH and temperature changes. With the rapid development of dual responsive (pH/temperature) hydrogels, and their applications in textiles as drug delivery systems will develop smart textiles in near future with more functionalities.

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